PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of:	Docket No: **Q101074**
Takashi HORIGUCHI et al.	Conf. No.: **9679**
Appln. No.: **10/547,843**	Group Art Unit: **1649**
Filed: **September 6, 2005**	Examiner: Chernyshev, Olga

For: **NOVEL PROTEIN AND ITS DNA**

APPEAL BRIEF UNDER 37 C.F.R. § 41.37

MAIL STOP APPEAL BRIEF - PATENTS
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In accordance with the provisions of 37 C.F.R. § 41.37, Appellant submits the following:

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I. REAL PARTY IN INTEREST

Takeda Pharmaceutical Company, Limited, Osaka, Japan.

II. RELATED APPEALS AND INTERFERENCES

There are not believed to be any other prior or pending appeals, interferences or judicial proceedings which are related to, will directly affect, or will be directly affected by or have a bearing on the Board's decision in the present appeal.

III. STATUS OF CLAIMS

Claims 1, 2, 4-7 and 17 are pending in the application. Claims 3, 8-16 and 18-36 are cancelled. All pending claims are currently rejected. This appeal is directed to rejected claims 1, 2, 4-7 and 17.

IV. STATUS OF AMENDMENTS

The Response Under 37 C.F.R. § 1.116 filed June 4, 2009, was entered, as indicated in the Advisory Action mailed June 10, 2009.

V. SUMMARY OF THE CLAIMED SUBJECT MATTER

Claims 1, 2, and 4 are independent claims.

Independent claim 1 recites an isolated protein, comprising the amino acid sequence of SEQ ID NO: 1, or a salt thereof. SEQ ID NO: 1 corresponds to the amino acid sequence of a protein called "C1". Specification, page 64.

Independent claim 2 recites an isolated protein or its salt, consisting of the amino acid sequence of SEQ ID NO: 1. SEQ ID NO: 1 corresponds to the amino acid sequence of a protein called "C1". Specification, page 64.

Independent claim 4 recites an isolated polynucleotide, comprising a polynucleotide encoding the protein comprising the amino acid sequence of SEQ ID NO: 1. Thus, claim 4 corresponds to the DNA encoding the amino acid corresponding to SEQ ID NO: 1, which corresponds to the amino acid sequence of a protein called "C1". Specification, page 64.

Independent claim 6 recites an isolated polynucleotide, consisting of the nucleotide sequence of SEQ ID NO: 2. SEQ ID NO: 2 corresponds to the nucleotide sequence of DNA encoding C1 protein. Specification, page 64.

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The grounds of rejection on appeal are whether the Examiner erred in rejecting claims 1, 2, 4-7 and 17 under 35 U.S.C. § 101 as allegedly lacking utility, 35 U.S.C. § 112, first paragraph as allegedly lacking enablement; and claim 17 under 35 U.S.C. § 112, second paragraph as allegedly being indefinite.[1]

[1] The rejections under 35 U.S.C. § 112 are contingent on the rejection under 35 U.S.C. § 101.

VII. ARGUMENT

The Examiner erred in rejecting claims 1, 2, 4-7 and 17 under 35 U.S.C. § 101, and § 112, first and second paragraph for at least the following reasons.

A. Claims 1, 2, 4-7 and 17 are Patentable Under 35 U.S.C. § 101

1. Utility Law

Under 35 U.S.C. § 101, "[w]hoever invents or discovers any new or useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent . . . ." The Patent Act, 35 U.S.C. § 101 (2000). Thus, patents may be granted for all inventions, including proteins and DNAs, that are useful, non-obvious, novel, and adequately disclosed. *Diamond v. Chakrabarty*, 447 U.S. 303 (1980).

Inventions must have substantial, specific and credible utility to be patentable. *Brenner v. Manson*, 383 U.S. 519, 534-35 (1996). Specific and substantial utility is synonymous with practical utility. *In re Fisher*, 421 F.3d 1365, 1371 (Fed. Cir. 2005). To satisfy the substantial utility requirement, an alleged use must have a significant and presently available benefit to the public. Id. The test of specific utility requires that an application disclose a use which is not so vague as to be meaningless. Id.

A specification which contains a disclosure of utility must be taken as sufficient to satisfy the utility requirement of § 101 unless there is a reason for one skilled in the art to question the objective truth of the statement of utility. *In re Langer*, 503 F.2d 1380 at 1391 (CCPA 1974) [Emphasis added], *In re Jolles,* 628 F.2d 1322 (CCPA 1980), . In *In re Brana* 51 F.3d 1560 (Fed. Cir. 1995), the Federal Circuit explicitly adopted the *Langer* standard as articulated in *In re*

Marzocchi 439 F.2d 220 (CCPA 1971), which indicates that the Office must presume that a statement of utility made by an applicant is true. See *Langer* at 1390-1392; *In re Malachowski* 530 F.2d 1402 at 1403-1405. Evidence of utility includes arguments, reasoning, or additional new evidence.

In *In re Brana* 51 F.3d 1560 (Fed. Cir. 1995) the court held that "a specification disclosure which contains a teaching of the manner and process of making and using the invention . . . must be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support." Id. at 1566. The PTO may establish a reason to doubt an invention's asserted utility only when the written description "suggests an inherently unbelievable undertaking or involves implausible scientific principles." [Emphasis added] *Id.*

In *Brana,* the Federal Circuit held that the disclosure of preclinical screening tests of compounds described as being "antitumor agents" was sufficient to establish practical utility where *in vitro* screening tests against known tumor model cell lines represented a specific disease against which the claimed compounds were alleged to be effective. Id. at 1565. Even in the absence of disclosure indicating that the compounds were useful in the treatment of any specific human disease, the court considered the utility of the compounds to be sufficiently disclosed where the "tumor models . . . contribute[d] to an increasing human cure rate." *Id.* at 1568. The court squarely rejected the PTO position that human clinical testing is necessary to establish practical utility for an invention having therapeutic utility. *Id.* at 1565; *cf. Scott v.*

Finney, 34 F.3d 1058, 1063 (Fed. Cir. 1994) (human testing in actual use circumstances was not required to establish a reduction to practice).

The PTO "Utility Examination Guidelines" are applicable to determinations of statutory utility and direct Examiners to focus on and be receptive to assertions made by Applicants that the invention is "useful" for a particular reason. *In re Fisher*, 421 F.3d 1365 at 1372; Utility Examination Guidelines, Federal Register, Vol. 66, No. 4, Friday, January 5, 2001. The PTO Guidelines state that a "well-established utility" is specific, substantial, and credible utility which can be implied by the specification's disclosure of the properties of a material, alone or taken with the knowledge of one skilled in the art. Guidelines, page 32. As stated by the Federal Circuit, "[t]o violate [35 U.S.C.] 101 the claimed [invention] must be totally incapable of achieving a useful result." *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 (Fed. Cir. 1992) (Emphasis added). Even "[a] small degree of utility is sufficient." *E.I. du Pont De Nemours and Co. v. Berkley and Co.*, 620 F.2d 1247, 1260 (8th Cir. 1980).

The USPTO Guidelines state clearly that an applicant need only provide *one* credible assertion of specific utility for any claimed invention to satisfy the utility requirement. Guidelines, page 32. Furthermore, the Guidelines state that an assertion of specific utility in the patent specification creates a presumption of utility. To overcome this presumption, the examiner must establish that it is more likely than not that one of ordinary skill would doubt the truth of the statement of utility. Id. If the applicant asserts that the claimed invention is useful for any particular purpose (*i.e.*, a specific utility), and that assertion would be considered credible by a person of ordinary skill, the examiner is *not* to impose a rejection based on lack of utility.

Furthermore, if the invention has a well established utility, regardless of any assertion made by the applicant, the examiner is not to impose a rejection based on lack of utility. Id. More particularly, the burden is initially on the examiner to make a *prima facie* showing that the claimed invention lacks utility, and to provide a sufficient evidentiary basis for factual assumptions relied on in establishing the *prima facie* case. Id.

The USPTO Guidelines make clear that evidence of pharmacological or other biological activity of a compound will be relevant to an asserted therapeutic use if there is a *reasonable* correlation between the activity in question and the asserted utility. Statistical *certainty* is not required. Also, there is no requirement for the applicant to provide evidence of success in treating humans even where such a utility is asserted.[2] It is improper for an examiner to request evidence of safety in the treatment of humans or the degree of effectiveness when used to treat humans.

2. The Lack of Utility Rejection

The lack of utility rejection, as best discerned, is premised on the following Office arguments of record.

In the non-final Office Action mailed May 11, 2007 the Examiner asserts, "the instant application does not disclose a specific biological role for this protein or its significance to a particular disease, disorder or physiological process, which one would wish to manipulate for a

[2] The USPTO legal analysis also emphasizes that any combination of evidence from *in vitro* or *in vivo* testing can be sufficient to establish the credibility of an asserted utility. More particularly, if reasonably correlated to the particular therapeutic or pharmacological utility, data generated using *in vitro* assays, or from testing in an animal model or a combination thereof, should be sufficient.

desired clinical effect". Page 3. The Examiner indicates that because the claimed polypeptide is allegedly not associated with a particular disease or disorder and because one would not believe that the claimed polypeptide would "prevent or treat a condition or disease"...the specification fails to disclose a utility. Office Action mailed May 11, 2007, pages 5 and 6. At page 4 of the Office Action, the Examiner cites *Brenner v. Manson* asserting, "the instant situation is directly analogous to that which was addressed..." Id. No other law is cited to support the Examiner's position in this Office Action.

In the final Office Action mailed October 10, 2007, the Office modifies the lack of utility rejection made in the non-final Office Action mailed May 11, 2007 to include the argument that because the specification allegedly fails to disclose statistical significance, working examples using cells transfected with genes that are not claimed by Applicants and allegedly fails to explain how spontaneous secretion of Aβ in cells transfected with C1 relates to etiology of Alzheimer's disease, the lack of utility rejection is maintained. In the Office Action mailed October 10, 2007, the Office cites *In re Fisher* for the first time, which the Examiner characterizes as directly analogous. Id. page 5.

In the non-final Office Action mailed March 7, 2008, at page 6, the Examiner cites *Brenner v. Manson* asserting, "Characterization of the claimed nucleic acids of SEQ ID NO:2 and encoded protein SEQ ID NO:1 as affecting secretion of Aβ or survival of cells artificially transfected with the protein is clearly not sufficient to establish their utility."

In the final Office Action mailed March 7, 2008, the Office acknowledges the legal requirement "that the patent application describes the utility of the claimed invention based on

evidence or obviousness to one skilled in the art" but ignores Applicants' evidence and applies a legally unsupported standard, stating, "there is no disclosure that the instant polypeptides or polynucleotides can be used as a marker for AD, or that the polypeptide of SEQ ID NO:1 can be used for therapeutic purposes to treat AD...the results of experiments performed on cells with artificially altered genotype do not make it immediately obvious for one skilled in the art that instant C1 protein has a specific role in the etiology of AD...[and]...there is no record of suppression of Aβ secretion upon administration of C1." [Emphasis added] Office Action mailed March 7, 2008, pages 3 to 4.

In summary, the lack of utility rejection is premised, as best can be discerned from the record, on Applicants allegedly not having experimentally proven a role for C1 in physiology or pathophysiology (i.e., use of C1 to achieve a desired *clinical* effect). The rejection is also based on the allegation that Applicants have not demonstrated that C1 is therapeutic. Further, the rejection is premised on the allegation that Applicants have not proven that C1 has a role in the etiology of Alzheimer's disease (AD), have not included statistical significance and have not used humans (i.e., suppression of Aβ upon *administration*).

3. The Record Shows That Claims 1, 2, 4-7 and 17 Have A Utility Under 35 U.S.C. § 101

The Examiner erred in rejecting claims 1, 2, 4-7 and 17 on technical and legal grounds. Applicants have clearly established, on the record, the nexus between C1 protein (i.e., SEQ ID NO: 1) and enhanced expression in nerve cells subjected to endoplasmic reticulum (ER) stress. Applicants have further established, as the Examiner admits, that the expression of C1 is

enhanced in rat primary nerve cells that have been stimulated with J3 amyloid. *See* Office Action mailed June 10, 2009, pages 2-4. Applicants have clearly established that C1 promotes cell death in SK-N-AS cells (*human* neuroblastoma) and that C1 inhibits secretion of A1340 and A1342 in IMR-32 cells (*human* neuroblastoma). Office Action mailed June 10, 2009, pages 2-4.

Indeed, the Office does not dispute Applicants' evidence of utility. First, in the Office Action mailed March 5, 2007, the Office admits that the specification teaches that C1 was discovered by exhaustive analysis of gene expression in nerve cells against endoplasmic reticulum stress and that C1 regulates repair and decomposition of abnormal proteins neuronal death and amyloid production because its expression is increased upon application of endoplasmic reticulum stress to nerve cells. Page 5. The Office admits, "the examples using rat primary nerve cells show changes in C1 gene expression in response to differential experimental conditions, pp. 65-67 [of the specification]". Office Action mailed March 5, 2007, page 5.

Second, in the Office Action mailed May 7, 2008, the Examiner admits that "Example 4, p.69 of the instant specification demonstrates that cells transfected with C1 gene had increased survival rate as compared to control cells (See Figures 1 and 2)" and "...Example 5, p. 69 of the instant specification describes results of experiments, in which cells transformed with C1 gene were recorded to secrete less Aβ than control cells..." Office Action mailed May 7, 2008, page 4. The Examiner also indicated that she did not doubt the Declaration testimony of Tomomichi Watanabe, wherein highly statistically significant data was provided, supportive of explicit utility in Applicants' specification (e.g., *see* Figures 1 and 2, page 3 of the Declaration Under 37 C.F.R. § 1.132 filed March 6, 2008). Office Action mailed May 7, 2008, page 6. The Office

acknowledges Applicants' evidence but accords it no weight, for reasons undisclosed in the record.

The utility of Applicants' claimed invention is also confirmed by prior art evidence. Applicants have pointed out that the state of art at the relevant time established a connection between Alzheimer's disease and Aβ. *See* Seubert *et al.*,[3] made of record by Applicants on October 28, 2008. The experimental results of decreased secretion of Aβ from cells transfected with C1 proves the specific, substantial and credible utility of the claimed protein to diagnose and treat Alzheimer's disease. Further, Siemers et al. and Fleisher et al.[4] report the use of the compound LY450139 (an inhibitor of γ-secretase, the enzyme that is involved in producing Aβ peptide from APP), having Aβ secretion inhibitory activity, as a therapeutic agent for Alzheimer's disease in clinical trials. *See* Siemers et al. and Fleisher et al., made of record by Applicants on October 28, 2008.

The Office relies on *In re Fisher* to support its position that the alleged lack of knowledge as to the biological function of SEQ ID NO: 1 or its relevance to AD renders the claims unpatentable. Office Action mailed October 10, 2007, page 5. But its reliance is misplaced and thus improper. In *Fisher*, the applicants argued that the claimed expressed sequence tags (ESTs) had utility as a nucleotide sequence alone, such as a research tool for monitoring gene expression

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[3] Peter SEUBERT et al., "Isolation and quantification of soluble Alzheimer's β-peptide from biological fluids", Nature, 1992, 359: 325-327.

[4] Adam S. FLEISHER, MD. et al., "Phase 2 Safety Trial Targeting Amyloid β Production with a γ-Secretase Inhibitor in Alzheimer Disease", Arch Neurol, 2008, 65(8): 1031-1038.

by measuring the level of mRNA through microarray technology and in identifying the presence or absence of polymorphisms. The proteins encoded by the ESTs were not ascribed a predicted function based on sequence similarity to known cDNAs, and the utility of the ESTs was not argued with regard to utility of the proteins encoded by the ESTs. Accordingly, the finding of a lack of utility in *In re Fisher* for ESTs which encode proteins without any predicted function is factually distinct from the instant case. In agreeing with the Board that the five claimed EST compounds were not shown to have a "specific" and "substantial" utility, the Federal Circuit concluded that "the claimed ESTs can only be used as research intermediates in the identification of underlying protein-encoding genes of unknown function." The panel majority thus analogized ESTs to compounds that are useful as intermediates in preparing other compounds that have no known utility other than such "nebulous" properties as "biological activity."

In the present application, Applicants' teachings are not mere disclosure of a DNA fragment corresponding to a polynucleotide sequence to a putative polypeptide with no known function (as did Fisher's). The evidence of record provides detailed information about the claimed subject matter, such as full and novel C1 polypeptides, full and novel DNAs, expression analysis, differential expression in specific tissues and cells, differential expression in specific tissues and cells under specific cellular conditions, highly specific relations between cell state and C1, and inhibitory activity by C1 against Aβ secretion. Applicants' polypeptide and DNA are not ESTs to compounds that are useful as intermediates in preparing other compounds that have no known utility other than such nebulous properties as biological activity. On the facts alone, *Fisher* is inapposite to the present appeal.

Similarly, the Office improperly relies on *In re Brana* to support its lack of utility rejection. The basis for rejection in *Brana* was that the specification failed to describe any specific disease against which the claimed compounds were active. The examiner concluded that the prior art tests (performed by Paull) and the tests disclosed in the specification (activity against human tumor cells *in vitro*) were not sufficient to establish a reasonable expectation that the claimed compounds had a practical utility (*i.e.*, antitumor activity in humans). During prosecution of the application, the applicants submitted a declaration under 37 C.F.R. §1.132 showing the antitumor activity of several compounds and the resultant expectation that the compounds would likely be clinically useful. The applicants appealed the final rejection to the Board of Appeals, who affirmed.

On appeal, the Federal Circuit found the applicants' comparison of the claimed compounds to the prior art (Paull compounds) sufficient to demonstrate that the claimed compounds were highly useful against leukemia. Based thereon, the court held that in light of the specification and prior art, applicants had shown a substantial and specific utility. In *Brana* the Examiner provided technical references (unlike in the present application) to attempt to buttress the lack of utility rejection. However, the court in *Brana* found that the references did not question the usefulness of any compound as an antitumor agent or provide any other evidence to cause one of ordinary skill in the art to question the asserted utility. The court also noted that the purpose of treating a complex cancer with chemical compounds did not suggest an inherently unbelievable undertaking. In reaching its decision, the court stated that human testing was not required but rather, Applicants' preclinical experimental testing would have been

sufficient to rebut a *prima facie* case of lack of utility. In fact, the court admonished the Office not to confuse the requirements for obtaining government approval to market a drug (testing for safety and effectiveness) with the requirements for obtaining a patent. In this regard, the court stated:

> Usefulness in patent law, and in particular in the context of pharmacological inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans. Were we to require Phase II testing in order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer.

The court acknowledged that under well-settled CCPA precedent, proof of an alleged pharmaceutical property for a compound by appropriate, statistically significant tests was sufficient to establish utility. Specifically, an applicant who has taught the public that a compound exhibits some desirable pharmaceutical property in a standard test has made a significant and useful contribution to the art, *even though it may eventually appear that the compound is without value in the treatment of humans.*

As discussed above, the instant application discloses detailed functional methods so as to allow one of ordinary skill in the art to use Applicants' teachings to arrive at numerous embodiments by conducting mere routine experimentation. A person of ordinary skill in the art would immediately appreciate that Applicants' invention is useful based on the properties disclosed. Given the nexus between C1 protein and enhanced expression in nerve cells subjected to endoplasmic reticulum stress; enhanced expression of C1 in nerve cells stimulated with J3

amyloid; C1 promotion of cell death in human neuroblastoma; and C1 inhibition of secretion of A1340 and A1342, one having ordinary skill in the art would appreciate a relationship between C1 and Aβ secretion processes. In addition, based on the state of the art, a connection between AD and Aβ (Seubert *et al.)* and the clinical trails for compound LY450139 (having the Aβ secretion inhibitory activity) as a therapeutic agent for Alzheimer's disease (Siemers et al. and Fleisher et al.) make apparent a well established utility for Applicants' invention. Applciants need not test the claimed invention in humans. Rejections under 35 U.S.C. § 101 (and 35 U.S.C. § 112, first paragraph) given the facts are improper and should not be imposed. *In re Folkers*, 344 F.2d 970 (CCPA 1965).

Based upon the law, and for at least the forgoing reasons, there is sufficient evidence that the claimed protein has a well-established or specific, substantial, and credible utility for, *inter alia*, C1.

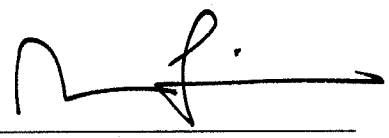
II. Claims 1, 2, 4-7 and 17 are Patentable Under 35 U.S.C. § 112, First and Second Paragraph

In paragraph 7, on page 5 of the Office Action, the Office rejects claims 1, 2, 4-7 and 17 under 35 U.S.C. § 112, first paragraph. Specifically, the Examiner states that the rejection under 35 U.S.C. § 112, first paragraph is contingent on the rejection under 35 U.S.C. § 101, addressed above. Thus, for the reasons discussed above, in Section I, the Examiner erred in making the rejection and the rejection should be withdrawn.

In paragraph 9, on page 5 of the Office Action, the Office maintains the rejection of claim 17 under 35 U.S.C. § 112, second paragraph. The Office's rejection is premised on the

allegation that the C1 protein is not sufficiently characterized (citing to the reasoning in Section 5 of the pending Office Action), which according to the Examiner is contingent on the rejection under 35 U.S.C. § 101. Thus, for the reasons discussed above, in Section I, the rejection should be withdrawn.

Respectfully submitted,



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Date: August 4, 2009

CLAIMS APPENDIX

CLAIMS 1, 2, 4-7 and 17 are on Appeal:

Claim 1. An isolated protein, comprising the amino acid sequence of SEQ ID NO: 1, or a salt thereof.

Claim 2. An isolated protein, consisting of the amino acid sequence of SEQ ID NO: 1, or a salt thereof.

Claim 3. (Cancelled).

Claim 4. An isolated polynucleotide, comprising a polynucleotide encoding the protein comprising the amino acid sequence of SEQ ID NO: 1.

Claim 5. The polynucleotide according to claim 4, which is DNA.

Claim 6. An isolated polynucleotide, consisting of the nucleotide sequence of SEQ ID NO: 2.

Claim 7. A recombinant vector, comprising the polynucleotide according to claim 5.

Claims 8-16. (Cancelled).

Claim 17. A kit for screening a compound or its salt that promotes or inhibits the activity of the protein or its salt according to claim 1, which comprises the protein or its salt according to claim 1.

Claims 18-36. (Cancelled).

EVIDENCE APPENDIX:

None.

RELATED PROCEEDINGS APPENDIX

None.